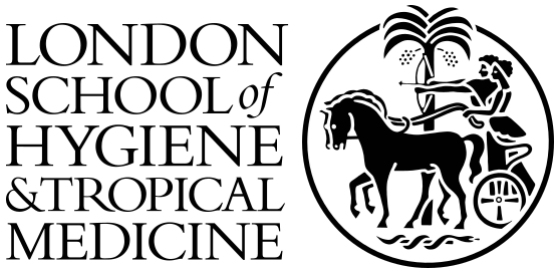

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Article

Metformin use and gastric cancer risk in diabetic patients after *Helicobacter pylori* eradication

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ABSTRACT

Background: Although prior studies showed metformin could reduce gastric cancer (GC) risk in patients with diabetes mellitus (DM), they failed to adjust for *Helicobacter pylori* infection and glycemic control. We aimed to investigate whether metformin reduced GC risk in *H. pylori* -eradicated diabetic patients and its association with glycemic control.

Methods: This was a territory-wide cohort study using hospital registry database, recruiting all diabetic patients who were prescribed clarithromycin-based triple therapy for *H. pylori* infection from 2003 to 2012. Subjects were observed from *H. pylori* therapy prescription until GC diagnosis, death or end of study (December 2015). Exclusion criteria included GC diagnosed within first year of *H. pylori* therapy, prior history of GC or gastrectomy, and failure of *H. pylori* eradication. The hazard ratio (HR) of GC with metformin (defined as at least 180-day use) was estimated by Cox model with propensity score adjustment for covariates (age, sex, comorbidities, medications [including insulin], and time-weighted average hemoglobin A1c [HbA1c]). All statistical tests were two-sided.

Results: During a median follow-up of 7.1 years (IQR:4.7–9.8), 37 (0.51%) of 7,266 diabetic patients developed GC at a median age of 76.4 years (IQR: 64.8–81.5 years). Metformin use was associated with a reduced GC risk (adjusted HR:0.49; 95% CI:0.24–0.98). There was a trend towards a lower GC risk with increasing duration (p_{trend} =0.01) and dose of metformin (p_{trend}=0.02). HbA1c level was not an independent risk factor for GC.

Conclusions: Metformin use was associated with a lower GC risk among *H. pylori* -eradicated diabetic patients in a duration- and dose-response manner, which was independent of HbA1c level.

INTRODUCTION

Gastric cancer (GC) is the fifth commonest cancer and the third leading cause of cancer-related mortality worldwide.(1) *Helicobacter pylori (H. pylori)* infection is the major risk factor for GC(2). However, *H. pylori* eradication could only reduce GC risk by approximately 40% (3-5). Apart from *H. pylori*, diabetes mellitus (DM) has been reported to increase GC risk by approximately 20%.(6) As DM is a very prevalent medical condition with more than 12% of adult population being affected,(7) the burden of GC cases attributed to DM could be substantial.

Metformin, a biguanide, is frequently used to treat DM. Apart from its effect on glycemic control, metformin has anti-cancer effect associated with insulin sensitization, reducing hyperinsulinemia and insulin-growth factor (IGF) production, both of which shown to enhance proliferation of cancer cells that express IGF receptors.(8) Metformin also activates AMP-activated protein kinase (AMPK) which suppresses cancer cell growth by inhibiting the mammalian target of rapamycin pathway.(9) The chemopreventive role of metformin in GC, however, remains controversial. While no association between metformin use and GC was reported by some studies,(10, 11) others suggested a protective effect with varying effect estimates.(12-16) A recent meta-analysis(17) concluded that metformin decreased GC risk by 24% but there was a statistically significant heterogeneity among studies. More importantly, other important risk factors of GC including *H. pylori* infection

and DM severity have not been adequately addressed in previous studies, potentially undermining the role of metformin on GC prevention.(17) As *H. pylori* is the most important risk factor of GC, failure to stratify patients according to *H. pylori* status will affect the true effect estimate of metformin on GC development. Moreover, GC risk was shown to be higher among individuals with higher hemoglobin A1c (HbA1c) levels(18). The beneficial effect of metformin on reducing GC could be mediated via improving DM control rather than the proposed anti-cancer mechanisms.

With the use of a large cohort of diabetic patients who had received *H. pylori* eradication therapy, we aimed to investigate the potential chemopreventive effect of metformin on GC in diabetic patients who had received *H. pylori* eradication therapy, and whether higher HbA1c level was associated with an increased GC risk.

METHODS

Data source

This was a territory-wide cohort study using data retrieved from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The Hospital Authority is the governing body of all public hospitals and clinics in Hong Kong with a population of 7.3 million, and a 90% coverage of all primary, secondary and tertiary care during the study period (2003–2015).(19) Patient's data including demographics, diagnoses,

drug dispensing records, procedures and laboratory results, hospitalization, attendance of outpatient clinics and emergency departments, and death are all accessible in the CDARS.(20-25) Diagnoses are coded in accordance with the International Classification of Diseases, Ninth Revision (ICD-9). Prior studies using this electronic registry database showed high coding accuracy with positive and negative predictive values of > 90.(21, 26) Individuals' information is anonymized with a unique reference key to protect patient's confidentiality. The study was approved by the Institutional Review Board of the University of Hong Kong and the West Cluster of Hospital Authority, Hong Kong (reference no: UW 16-545).

Study Subjects

All adult patients aged 18 years or above with a baseline diagnosis of DM who were dispensed a course of clarithromycin-based triple therapy for *H. pylori* between 1 January 2003 and 31 December 2012 were identified. The diagnosis of DM was based on the ICD-9 codes of DM (ICD-9 codes: 249 and 250). The prescription of clarithromycin-based triple therapy included the co-prescription of one of the proton pump inhibitors (PPIs) with clarithromycin and either amoxicillin or metronidazole with the correct doses, same prescription start dates and a treatment duration of 7-14 days.(27) With the high *H. pylori* eradication rate (> 90%) and low resistance rate to clarithromycin (8%) in Hong Kong(28),

clarithromycin-based triple therapy was the first-line *H. pylori* treatment during the study period.(29) A diagnosis of *H. pylori* infection was made by either biopsy-based tests (rapid urease test and histology) or urea breath test, as other diagnostic modalities were not available in the public hospitals. Exclusion criteria included: gastric lymphoma; GC diagnosed within the first year of *H. pylori* eradication therapy (as there was a possibility of delayed or missed diagnosis); prior history of GC; prior gastrectomy; and failure of *H. pylori* eradication. Because there was no ICD-9 code for failure of *H. pylori* eradication, this could only be inferred from the repeated prescription of clarithromycin-based triple therapy, or subsequent prescriptions of either a second-line therapy (either PPI-levofloxacin-amoxycillin or bismuth-based quadruple therapy), or a third-line therapy (rifabutin-based therapy). The patient selection process is illustrated in **Supplementary Figure 1**.

Study Outcome

Gastric adenocarcinoma after *H. pylori* eradication therapy was identified by the ICD-9 coding (**Supplementary Table 1**). The validation of the GC diagnosis and final *H. pylori* status of these cancer patients had been validated in our previous studies, with 100% accuracy.(30) The observation period started from the first date of *H. pylori* therapy prescription (i.e. index date), and censored at GC diagnosis, death or end of study (December

2015). The earliest date of hospitalization for cancer workup or treatment was regarded as the GC diagnosis date.

Metformin, insulin and other covariates

We defined metformin use as more than 180-day use [as proposed by Kim et al(13)] after receiving *H. pylori* eradication therapy. To study the dose-response relationship of metformin on GC risk, cumulative defined daily dose (cDDD) as per the World Health Organization Collaborating Center for Drug Statistics Methodology (31) was calculated by summing the dispensed DDDs of metformin during the study observation period, and categorized into non-metformin use, use of cDDDs below the median, and use of cDDDs equal to or above the median. To study the duration-response relationship, the duration of metformin use was divided into three groups: non-metformin use, <3 years, and ≥3 years, as defined previously by Kim et al.(13)

Potential risk factors for GC included the age of receiving *H. pylori* eradication therapy, gender, smoking and alcohol use, past history of peptic ulcer disease, other comorbidities (atrial fibrillation, ischemic heart disease, congestive heart failure, chronic renal failure, cirrhosis, stroke, dyslipidemia, hypertension and obesity) and concurrent medications uses (aspirin, non-steroidal anti-inflammatory drugs [NSAIDs], cyclooxygenase-2 [COX-2] inhibitors,(32, 33) statins,(34) PPIs,(30, 35) insulin(36, 37)) and HbA1c(18) were

considered during analysis. Smoking and alcohol statuses were ascertained as reported previously.(38) Smoking was identified by the documentation of the smoking status in the CDARS, the ICD-9 code of V15.82 or indirectly by the presence of chronic obstructive pulmonary disease (COPD). Alcohol use was signified by the presence of alcohol-related diseases, comprising gastrointestinal, hepatic, psychiatric and neurological diseases. Obesity was identified by the ICD-9 codes of 278.0 and 278.1 or a body mass index ≥25 kg/m^2. **eTable 1** shows the diagnostic codes of all variables. In order to adjust for the bias due to irregular interval measurements, time-weighted average HbA1c was used to represent the overall glycemic control during the observation period as described by Yip et al.(39) This was derived as the average HbA1c weighted by the time interval between successive measurements. We categorized the time-weighted average HbA1c into a binary variable by a cut-off value of 7% as individuals with HbA1c ≥7% were at a higher risk of GC than subjects without DM in a previous population-based cohort study.(18) For consistency, we used a cut-off of 180 days to define the use of other medications. We also investigated the association between insulin use and GC, as IGFs have been proposed to be involved in GC development.(36, 37, 40)

Statistical analyses

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing) statistical software. Continuous variables were expressed as median with interquartile range (IQR) and categorical variables were presented as number (percentage). Comparison of two groups was analyzed by Mann-Whitney U-test for continuous variables, and Chi-square or Fisher's exact test for categorical variables. The Cox proportional hazards model was used to determine the hazard ratio (HR) of GC with metformin use. We checked whether the Cox proportional-hazard assumption was fulfilled by a 'complementary log-log'-scaled Kaplan-Meier plot and schoenfeld residuals (p-value > 0.05; which indicated no interaction of the covariates with time).

Propensity score (PS) adjustment was used to control for selection bias due to different baseline characteristics. The PS was estimated by multivariable logistic regression based on the aforementioned covariates, and represents the probability of prescribing metformin to an individual given the covariates. As such, any difference in GC risk would be due to metformin effect only. The PS distributions between metformin and non-metformin groups were compared graphically, showing no statistically significant areas of non-overlap which would otherwise violate the assumption of PS analysis (**Supplementary Figure 2**)(41).

The primary analysis was Cox regression with PS adjustment. The PS adjusted absolute difference in GC risk between metformin and non-metformin users was calculated as follows: (adjusted HR – 1) x (crude incidence rate of GC in non-metformin users).(42)

Sensitivity analysis was conducted to assess robustness of the results, including multivariable analysis, PS adjustment after trimming of individuals in the non-overlapping parts of PS distribution,(43) PS weighting by inverse probability treatment weighting (IPTW) with stabilisation,(44) and PS matching without replacement in a 1:1 ratio.(45) The description of these PS analysis methods was detailed in **Supplementary Table 2**. Standardised difference was used to assess the balance of the covariates between the two groups before and after IPTW and PS matching, and a value of below 0.2 indicated a negligible difference.(46) **Supplementary Table 3** shows that most of the covariates were balanced after either IPTW or PS matching. **Supplementary Figures 2 and 3** also show that PS distriubtion between the two groups became largely similar after PS matching.

Similar statistical analyses were performed to determine the association between insulin use and GC. A two-sided p-value of < 0.05 was used to define statistical significance. The R packages 'survival' and 'MatchIt' were used for Cox regression analysis and PS matching, respectively.

RESULTS

Patient characteristics

A total of 7,266 diabetic patients (type I: 30, type II: 3,394, unclassified: 3,842) who had received *H. pylori* eradication therapy during the study period were included. The median age

of receiving clarithromycin-based triple therapy was 65.2 years (IQR:56.1–74.2), and 52.0% were male. There were 5,368 (73.9%) metformin users and the use of other diabetic medications was shown in **Table 1**.

Risk of gastric cancer development and data validation

During a median follow-up of 7.1 years (IQR: 4.7–9.8 years) (**Table 1**) totalling 52,208 person-year, 37 (0.51%) patients were diagnosed to have GC (incidence rate: 7.1 per 10,000 person-years), with 21 (56.8%) in the non-cardia region, 12 (32.4%) in the cardia and unspecified sites in the remaining 4 (10.8%) cases. The median age at GC diagnosis was 76.4 years (IQR: 64.8–81.5 years). The median duration from receiving *H. pylori* eradication therapy to GC development was 4.4 years (IQR:3.1–6.8; metformin group: 5.1[IQR:3.5–7.6] vs non-metformin group: 3.9 [IQR:1.8–6.2]; p=0.117) (data not shown).

Effect of metformin, insulin, and HbA1c on gastric cancer risk

The median duration of metformin use was 5.5 years (IQR:3.3–8.4), and the median cDDD was 975 (IQR:436–1837). Among metformin users, 20 (0.37%) developed GC with an incidence rate of 4.9 per 10,000 person-years. There was a statistically significantly lower GC risk among metformin users (PS adjusted HR: 0.49; 95% CI:0.24–0.98) (**Table 2**). Sensitivity analysis by different statistical methods showed similar results (**Table 2)**. The PS adjusted

absolute risk difference between metformin and non-metformin use was 7.60 fewer cancer cases (95% CI:0.30–11.33) per 10,000 person-years (data not shown). When patients with type I DM were excluded (n=7,236, GC =36), the PS adjusted HR was 0.47 (95% CI:0.23–0.96).

A total of 2,075 (28.6%) diabetic patients used insulin (**Table 1**). The median duration of insulin use was 4.7 years (IQR:1.3–7.2; metformin group: 4.7 [IQR:1.2–10.1] vs non-metformin group: 4.9 [IQR:1.4–11.8]. The PS adjusted HR of GC with insulin use was 0.81 (95% CI:0.35–1.85) (data not shown)**.**

In total, 11,286 HbA1c measurements were taken at baseline and during follow-up with a median of 13 measurements (IQR:7–22 times) per patient at a median interval of 4.7 months (IQR:3.4–7.9) (data not shown). For the whole cohort, the median baseline and time-weighted averaged HbA1c were 7.3% (IQR:6.5–8.7%) and 7.2% (IQR:6.6–7.9%), respectively. A higher proportion of metformin users had time-weighted HbA1c level ≥7% than non-metformin users (64.0% vs 39.7%) (**Table 1**). The corresponding median level of baseline HbA1c in the metformin and non-metformin groups was 7.4% (IQR: 6.6–8.9%) and 6.8% (IQR: 6.1–8.0%), whereas the time-weighted averaged HbA1c was 7.3% (IQR: 6.8–8.0%) and 6.7% (IQR: 6.2–7.6%), respectively (data not shown). Compared to patients with a time-weighted average HbA1c level of <7%, patients with a higher level did not have an

increased GC risk on either unadjusted (HR 0.83; 95% CI: 0.60–1.15) or multivariable analysis (HR 1.60; 95% CI: 0.78–3.27) (**Table 3)**.

Duration- and dose-response of metformin use and gastric cancer

Table 4 shows the duration- and dose-response between metformin use and GC. A longer duration of metformin use was associated with a lower GC risk (HR: 0.85; 95% CI:0.74–0.96) for every one year increase in use. Compared with non-metformin users, those who used metformin for <3 years and ≥3 years had HRs of 0.75 (95% CI:0.32–1.74) and 0.35 (95% CI:0.16–0.80), respectively (p_{trend}=0.01). For dose effect, the HRs of GC with metformin use for <975 cDDD (median cDDD) and ≥975 cDDD, when compared with non-metformin use, were 0.73 (95% CI:0.35–1.53) and 0.33 (95% CI:0.13–0.86), respectively (p_{trend}=0.02).

DISCUSSION

In this territory-wide cohort study including more than 7,200 diabetic patients who had *H. pylori* eradicated, we showed that metformin use was associated with a 51% reduction in GC risk, with a clear dose- and duration-gradient association. Since GC risk was found to be 20% higher among diabetic patients(6) and eradication of *H. pylori* could only reduce GC risk by about 40%,(3, 4) there is a genuine need to identify novel chemopreventive agents for this specific group of high-risk patients.

The beneficial effects of metformin on GC prevention remains controversial as randomized clinical trials were lacking and previous observational studies yielded conflicting results.(10-16) Apart from the heterogeneity on definition of drug exposure, comparators and study design, failure to adjust for other important risk factors of GC including *H. pylori* infection, HbA1c level and concurrent medication use is likely the reason.(17) To address these limitations, our study included only diabetic patients who were successfully treated for *H. pylori* at baseline. This would remove the most important risk factor of *H. pylori* infection that could affect the effect estimate of metformin on GC risk. By including the time-weighted average HbA1c level into analysis, our study not only considered the baseline HbA1c level but also the dynamics of DM control throughout the follow-up so that a more precise effect estimate could be derived. In our study, a higher time-weighted average HbA1c level of ≥7% was not an independent risk factor for GC after *H. pylori* eradication. In contrary, a Japanese population-based cohort study showed that a higher HbA1c level acted synergistically with *H. pylori* infection in increasing GC risk(18). Notably, their study cohort differed from our current cohort of *H. pylori*-eradicated subjects, and no adjustments were made on the use of concurrent medications that could modulate GC risk, such as aspirin/NSAIDs(32), statins(34) and PPIs(35).

We found that HbA1c levels were actually higher among metformin users, possibly related to the poor glycemic control necessitating metformin use. Yet, GC risk was

statistically significantly lower in the metformin group. Hence, our findings support the biological mechanisms underlying metformin in preventing GC, which is not mediated through improving glycemic control. Notably, although IGFs have been linked to GC development(40), insulin treatment was not associated with an increased GC risk in this study. The duration- and dose-response association observed further strengthened the possible chemopreventive effect of metformin on GC. A longer duration of metformin use was associated with a lower GC risk, which was consistent with the study by Kim et al showing the chemopreventive effect was only evident after ≥3 years of metformin use.(13)

The strength of our study is the use of a comprehensive electronic public healthcare database that included drug prescription and dispensing records, reducing selection and information biases of observational studies.(32) The long follow-up duration (a median of 7 years) also enables the assessment of GC with a long lag time. The robustment of the result is verified by the consistency from sensitivity analysis using various PS analysis methods which adjusted for a wide array of covariates. Notably, metformin users had more cormobidities than non-metformin users (**Table 1**). Given than all these covariates are potential risk factors of GC, the protective effects of statin against GC could only be underestimated.

Several limitations of this study should be acknowledged. First, some risk factors like family history of GC and diet were not routinely captured in the CDARS. Second, as the success of *H. pylori* eradication was not documented in the ICD coding, we identified

patients with failure of clarithromycin-based triple therapy by the repeated prescription or prescription of second and third line therapies. Third, drug compliance could not be ascertained in this electronic database. However, medications are prescribed and dispensed together in the same hospital at a very low price (US$1.5 per item for 16 weeks), which can rule out the issue of non-dispensing due to cost issue. Further, non-compliance would only bias the beneficial effect of metformin towards null. Fourth, due to the long lag time and relatively low incidence of GC development after *H. pylori* eradication, there were only 37 GC cases. Stratified analyses according to the cancer location (non-cardia and cardia) could not be performed. Lastly, information on GC staging was not available in the CDARS, precluding the exploration of potential effect of metformin on GC staging.

In conclusion, our territory-wide study showed that among diabetic patients who had *H. pylori*-eradicated, metformin use was associated with a statistically significantly lower GC risk in a duration- and dose-response manner. This cancer protective effect was independent of glycemic control.

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Potential competing interests: WKL has received honorarium for attending advisory board meetings of AbbVie, Takeda and Abbott Laboratories.

Tables

Table 1. Baseline characteristics of study cohort (n=7,266)

Characteristic	All, No. (%) (n=7,266)	Metformin users, No. (%) (n=5,368)	Non-metformin users, No. (%) (n=1,898)
Median age at triple therapy, y (IQR)	65.2 (56.1 74.2)	63.8 (55.6-72.6)	69.7 (58.2–78.2)
Male sex	3779 (52.0)	2716 (50.6)	1063 (56.0)
Median duration of follow-up, y (IQR)	7.1 (4.7 – 9.8)	7.5 (5.2 – 10.1)	5.8 (3.5 – 8.8)
Time-weighted average HbA1c ≥ 7%	4191 (57.7)	3437 (64.0)	754 (39.7)
Smoking	1265 (17.4)	945 (17.6)	320 (16.9)
Alcohol	116 (1.6)	61 (1.1)	55 (2.9)
History of gastric ulcer	281 (3.9)	180 (3.4)	101 (5.3)
History of duodenal ulcer	295 (4.1)	198 (3.7)	97 (5.1)
Hypertension	4503 (62.0)	3246 (60.5)	1257 (66.2)
Dyslipidemia	1982 (27.3)	1483 (27.6)	499 (26.3)
Obesity	1288 (17.7)	1097 (20.4)	191 (10.1)
Ischemic heart disease	1864 (25.7)	1318 (24.6)	546 (28.8)
Atrial fibrillation	649 (8.9)	426 (7.9)	223 (11.7)
Congestive heart failure	1001 (13.8)	579 (10.8)	422 (22.2)
Stroke	1341 (18.5)	935 (17.4)	406 (21.4)
Chronic renal failure	770 (10.6)	346 (6.4)	424 (22.3)
Cirrhosis	274 (3.8)	148 (2.8)	126 (6.6)
Aspirin/ NSAIDs/COX-2 inhibitors*	3457 (47.6)	2649 (49.3)	808 (42.6)
Statins*	4375 (60.2)	3562 (66.4)	813 (42.8)
Proton pump inhibitors*	966 (13.3)	654 (12.2)	312 (16.4)
Insulin*	2075 (28.6)	1575 (29.3)	500 (26.3)
Sulphonylureas*	4004 (74.6)	4004 (74.6)	772 (40.7)
Acarbose*	279 (3.8)	239 (4.5)	40 (2.1)
Glitazones*	288 (4.0)	254 (4.7)	34 (1.8)
Dipeptidyl peptidase IV inhibitors*	842 (11.6)	781 (14.5)	61 (3.2)

HbA1c, hemoglobin A1c; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2;

* Drug use was defined as use for more than 180 days

Table 2. Association between metformin use* and gastric cancer (GC) risk

Analysis	No. of patients	No. of GC events	HR of GC with metformin use (95% CI)	p-value†
Unadjusted analysis	7266	37	0.32 (0.17 – 0.61)	< 0.001
Multivariable analysis	7266	37	0.46 (0.23 – 0.93)	0.03
PS adjustment (without trimming)	7266	37	0.49 (0.24 – 0.98)	0.045
PS adjustment after trimming	7253	37	0.49 (0.24 – 0.98)	0.045
PS weighting by inverse probability treatment weighting	7266	37	0.47 (0.23 – 0.96)	0.034
PS matching	3608	24	0.36 (0.15 – 0.87)	0.02

HR, hazard ratio; CI, confidence interval; PS, propensity score

*Metformin use was defined as use for more than 180 days

†Cox proportional hazards model was used to calculate the P values, and the test was two-sided.

Table 3. Association between metformin, insulin, time-weighted average HbA1c and gastric cancer risk

Variables	Unadjusted analysis		Multivariable analysis*	
	HR (95% CI)	p-value†	HR (95% CI)	p-value†
Metformin‡	0.32 (0.17 – 0.61)	< 0.001	0.46 (0.23 – 0.93)	0.03
Insulin‡	0.80 (0.38 – 1.70)	0.57	0.76 (0.33 – 1.75)	0.52
Time-weighted average HbA1c ≥ 7%	0.83 (0.60 – 1.15)	0.27	1.60 (0.78 – 3.27)	0.20

CI, confidence interval; HR, hazard ratio; HbA1c, hemoglobin A1c

* Adjusted for age at triple therapy, sex, smoking, alcoholism, history of gastric ulcer, history of duodenal ulcer, other comorbidities (hypertension, dyslipidemia, obesity, ischemic heart disease, atrial fibrillation, congestive heart failure, stroke, chronic renal failure, cirrhosis) and concurrent medications (statins, aspirin/non-steroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors, proton pump inhibitors)

†Cox proportional hazards model was used to calculate the P values, and the test was two-sided.

‡Drug use was defined as use for more than 180 days

Table 4. Association between duration and dose of metformin use and gastric cancer risk (propensity score adjustment)

Duration and dose	HR (95% CI)	p-value*	P_{trend}†
Duration			
Per every 1 yr increase in use‡	0.85 (0.74 – 0.96)	0.01	
Metformin use§			
Non-metformin users	1.00 (Reference)		
< 3 years	0.75 (0.32 – 1.74)	0.51	0.01
≥ 3 years	0.35 (0.16 – 0.80)	0.01	
Dose			
Non-metformin users	1.00 (Reference)	-	
< median, 975 cDDD	0.73 (0.35 – 1.53)	0.40	0.02
≥ median, 975 cDDD	0.33 (0.13 – 0.86)	0.02	

HR, hazard ratio; 95% CI, 95% confidence interval; cDDD, cumulative Defined Daily Dose

*****Cox proportional hazards model was used to calculate the P values, and the test was two-sided.

†**Cox** proportional hazards model was used to calculate the P values, and the test was two-sided.

‡Continuous variable

§Categorical variable